Molecular modelling of caffeine with betacyclodextrin complex was performed at the highest level of interaction

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Abstract:

The study suggests a high likelihood of creating a computer model for the betacyclodextrin complex and caffeine compound interaction. The integration of various caffeine compounds into the betacyclodextrin complex cavity was achieved through electrostatic attraction, resulting in a stable internal energy of -1543.726347 kilocalorie.

Keywords: caffeine, betacyclodextrin, total internal energy.

الملخص

كانت هذه الدراسة قد أعطت الأمكانية العالية في تكوين مذمج حوسبي بين متراكب البيتاسيكلوديكسرتين و مركب الكافيين و تمكنَا في هذه الدراسة من إدماج عدد مركبين من الكافيين في داخل تجويف متراكب البيتاسكيلوديكسترين بحيث كانت عدد 2 نماذج (A, B) حوسبية لإختيار أفضل نموذج فراغي يستقر داخل تجويف البيتاسيكلوديكسترين و أستقر الوضع علي إختيار النموذج A و من تم أضفنا مركب كافيين أخر و كانت النتائج جداً مستقرة داخلياً بالتجاذب الكهروستاتيكي و بنشاطية جيدة كانت عند طاقة داخلية = 1543.726347- كيلوكالوري.

1. Introduction:

Coffee is regarded as a symbol of generosity among Arabs due to its high caffeine content, which has a stimulating effect on humans. It contains chemical components that are linked to health benefits, and long-term consumption has been shown to reduce the risk of many chronic diseases, including type 2 diabetes, Parkinson's disease, and liver disease.[1]

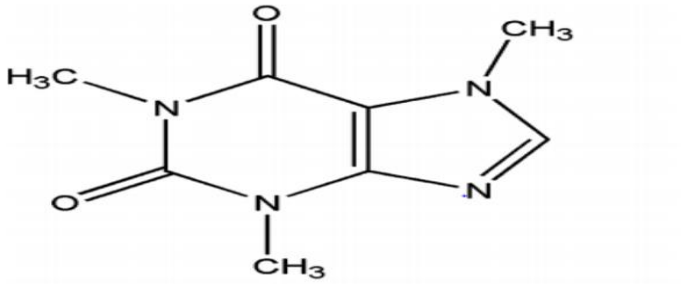


Figure 1. Structural formula of caffeine compound

Coffee is appreciated for its aroma and flavour due to its caffeine content and the presence of over a thousand different chemicals, including carbohydrates, fats, nitrogen, vitamins, minerals, alkaloids, and phenolic compounds. [2] It is a significant source of caffeine, which has been shown to have various behavioural effects. For instance, caffeine enhances alertness and improves sustained attention and psychological performance. These benefits often increase with dosage, within the limits consumed by the majority of the population. [3]

The coffee tree belongs to the Rubiaceae family and has several recognized species worldwide. Of these, only two are economically significant: Arabica

coffee, which accounts for approximately 70% of the global coffee market, and Robusta coffee.

In 2011, Brazil led the world in green coffee production, followed by Vietnam and Indonesia. The seeds from different countries or regions typically have distinct differences in flavour, aroma, body, and acidity. [4]

There are various types of coffee, each with different serving methods and additives depending on the country of origin. These include Arabic coffee, American coffee (commonly known as Nescafe), and Italian coffee, which consists of two types of espresso and cappuccino. While coffee provides minimal nutritional value, it contains numerous natural chemicals, including carbohydrates, fats, and various compounds. The fragment mentions nitrogenous compounds, vitamins, minerals, alkaloids, and phenolic compounds. Some of these compounds are potentially healthy, while others are potentially harmful. One of the most well-known compounds is caffeine. [5]

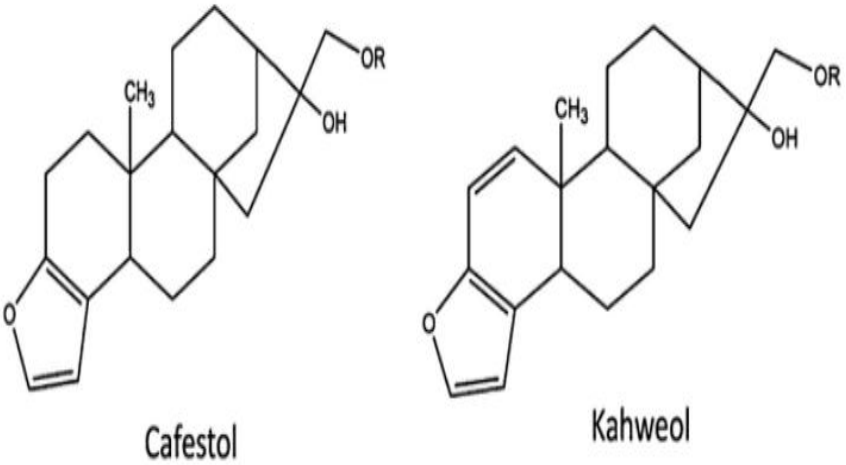
Caffeine is a widely used stimulant found in coffee, tea, cocoa, and chocolate. It belongs to the group of methyl xanthine stimulants and is most commonly consumed through coffee, which contains approximately 1-2% caffeine. Its effects are felt in both the heart and brain. Caffeine has various effects on the body, including increasing heart rate, mental activity, gastric juice secretion, and bronchi expansion in the lungs, as well as urine production. The amount of caffeine present in coffee varies depending on the type. Instant coffee, such as Nescafe, typically contains the highest percentage of caffeine. [6]

The percentage of caffeine decreases during intense coffee roasting. Caffeine is the primary component of coffee that determines tolerance or intolerance. In a healthy liver, the hepatic microsomal enzymatic system metabolizes most caffeine. Paraxanthine is the primary metabolite, with smaller amounts of theobromine and theophylline, while a small amount of unchanged caffeine is excreted in the urine. The metabolism of caffeine is dependent on the enzymatic system of the liver. Elderly individuals with a depleted enzymatic system may not be able to tolerate coffee containing caffeine, It is recommended that individuals with sensitive stomachs consume decaffeinated coffee, if at all, as both caffeinated and decaffeinated coffee can cause heartburn. Elderly individuals generally tolerate moderate coffee consumption. During the gradual heating process in the roasting machine, which involves a large rotating drum, the water remaining in each cell is converted into steam. This steam then triggers a variety of complex chemical reactions between the abundant sugars, proteins, lipids, and minerals present within the cells. Sugars combine with amino acids at high temperatures, typically ranging from 185 to 240 degrees Celsius, During the Maillard's reaction, peptides and proteins undergo caramelization, resulting in the formation of glycosylamine and melanoidins. These compounds give coffee its characteristic bittersweet taste and brown colour. It is important to note that this improved text adheres to the desired characteristics of objectivity, comprehensibility and logical structure, conventional structure, clear and objective language, format, formal register, structure, balance, precise word choice, and grammatical correctness. Roasted coffee also produces up to 12 liters of carbon dioxide per kilogram. No changes in content have been made. [7]

Caffeine can cause addiction, particularly when consumed regularly and in increasing amounts. To overcome addiction, some people opt for decaffeinated coffee. Abruptly stopping caffeine consumption can result in symptoms such as nausea and headaches, but these are usually manageable. Some athletes consume coffee as they believe it enhances their performance.

However, caffeine is considered a prohibited stimulant in the analysis. This also applies to drinking cola due to its caffeine content. Drinking four cups of coffee within 30 minutes before the match puts the player at risk of doping, as shown in medical tests. The same applies to drinking tea because it also contains caffeine, which is a stimulant substance. Chlorogenic acid is a biologically active compound present in coffee that inhibits the absorption of carbohydrates. It is also referred to as 5(-O-caffeoylquinic acid) and can range from 70-350 mg in a 200-ounce cup. A millilitre of coffee contains approximately 35-175 mg of caffeic acid. [8]

Coffee Arabica contains cafestol and cohyol (coffee lipids) with individual concentrations ranging from 0.1-7 mg/ml in coffee.



Cafestol Kahweol

Figure 2. Structural formula of Arabica coffee components (cafestol and cohyol) structures.

Cyclodextrins are cyclic compounds composed of seven glucose units. They are recognized for their ability to form covalent or non-structural inclusions with organic compounds. The cyclodextrin cavity is non-polar and consists of 80% dioxane. It provides a slightly alkaline environment due to the presence of glycosidic ethers. Cyclodextrins have numerous applications in the food industry. They are primarily used as carriers for molecular encapsulation of flavours, vitamins, and colours. Additionally, their complexing properties are used to eliminate the bitter taste of unsaturated fats in products such as alcoholic beverages or coffee. [9]

Coffee is a source of polyphenolic compounds that exert antioxidant activity. Its specific phenolic components include chlorogenic acids, which are a family of esters formed between quinic acid and several cinnamic acids, such as caffeic and ferulic. This study aims to investigate the effect of the phenolic composition of coffee origin with betaCD and compare the results with those obtained for well-known coffee drink components, such as chlorogenic, caffeic, ferrulic and coumaric acids. The study aims to deduce the molecular mechanisms for the formation of an inclusion complex of coffee origin phenolic acids with beta-cyclodextrin.

Were used the chemicals beta-cyclodextrin (betaCD) and phenolic acids, including Chlorogenic (5-caffeoyl quinic acid) (CHA), caffeic acid (CA), ferulic acid (FE), and p-coumaric and o-coumaric acids (p-CU and o-CU), were used. Water was used as a solvent in all studies, including the preparation of coffee drink samples. Absorption spectra were recorded on an

S1000 spectrometer (Ocean Optics) in the range of 200-600 nm, using a 1 cm quartz. Excitation and emission spectra were measured from 300 to 500 nm, with excitation at 330 nm. The experimental setup followed standard procedures [10]. Fluorescence data was recorded using a Shimadzu RF 5001 PC fluorimeter with a chamber thermostat cell. [10]

Computational models were constructed for complexes of beta-cyclodextrin (betaCD) with caffeic and chlorogenic acids (CHA) using the Pymol program, based on the 3D structure of beta-cyclodextrin. Four systems were built, consisting of two betaCD-CA and two betaCD-CHA complexes. In each group, the acid molecule was introduced into the ventral cavity of the betaCD from either the 'top' or 'bottom' side. The structures of the complexes were optimized through energy minimization in a vacuum. Next, the complexes were immersed in water with a sodium ion to neutralise the negative charge on the carboxyl group of the acid, and their structures in water were also optimized through energy minimization. [11]

2. Previous studies :

1. Coffee drink contains chlorogenic and cinnamic acids, which are powerful antioxidants. When coffee interacts with betacyclodextrin, it forms included complexes that affect the physical properties of the guest molecule. In this study, we examined the spectroscopic changes in phenols originating in coffee, specifically chlorogenic (CHA) and caffeic acids (CA), due to complexation with beta-cyclodextrin (betaCD) in aqueous solutions. The thermal properties and dynamics of the formed complexes were also studied. The position of each

phenol within the beta-cyclodextrin cavity was extracted using spectroscopic data (absorption), and the binding constants of the complexes were calculated. The data indicate the formation of a 1:1 complex between betaCD and CHA or CA. The thermodynamic parameters (DH, DS and DG) of complexity were calculated using the temperature dependence of the latter. All thermodynamic parameters had negative values, indicating that the formation of these inclusion complexes was a pyroptosis-driven process in which van der Waals forces and weak hydrogen bonding played an important role. The stability and energy of betaCD, CHA, and -CA complexes in the aqueous phase were confirmed by molecular modeling, which also provided information on the conformation and interaction of the atoms forming the complexes. The molecular mechanism of the complexes was characterized using experimental data.

2. Caffeine (CAF) is a biologically active substance with a broad range of functions that have been known since ancient times and are widely used today. Its main pharmacological effect is the stimulation of the central nervous system, which is due to its action as a simultaneous antagonist of Adenosine (Ado) on the membrane proteins, specifically adenosine A1 and A2a receptors. This work investigates the atomic-level mechanism behind this effect. The primary objective of computer modelling is to determine how the CAF molecule, which is relatively small and rigid, can compete with the Ado molecule for binding sites despite having limited opportunities to engage in strong particle interactions. This is due to the hydrogen centers and limited

conformational flexibility of the CAF molecule » To address this question, we used the molecular mechanics (MM) method to calculate the minimum interaction energy between CAF and Ado molecules and the transmembrane receptor domains involved in Ado binding. Our MM calculations showed that most conformations of the separated Ado molecules corresponded to the configuration of two intramolecular H-bonds. This conclusion was confirmed at the MP2/6-31G(d,p) and MP2/6-311++G(d,p) levels of initiation theory. At minimum interaction energy, both Ado and CAF form hydrogen bonds with more than three amino acid residues, limiting the possibility of Addo interactions with the hydrophilic amino acids of the receptor fragments. The energy values in this scenario are similar. Thus, two molecules with differing numbers of hydrophilic centres and conformational possibilities may exhibit similar energy levels when forming complexes with adenosine receptor fragments.

3. Although cyclodextrins (CDs) have been studied for over 100 years and can be found in at least 35 pharmaceutical products, they are still considered new pharmaceutical excipients. CDs are oligosaccharides that possess biological properties similar to their linear counterparts, but their physicochemical properties differ. CDs are capable of forming water-soluble drug-like complexes with many poorly soluble drugs. CDs are used to enhance the aqueous solubility of drugs and improve drug bioavailability, for example, after oral administration. CD and poorly soluble drugs can be formulated as aqueous enteric solutions, nasal sprays, and eye drop solutions. Oligosaccharides are

recognized as non-toxic and pharmacologically active excipients for both drugs and food products. CD and CD complexes have been observed to self-assemble into nanoparticles, which can aggregate to form microparticles under certain conditions. These characteristics have influenced the way in which we conduct research on cyclodextrins (CDs) and have led to new opportunities for CD crafting. This review focuses on the pharmaceutical applications of CDs, with particular emphasis on their dissolution properties, tendency to self-assemble into aggregates, CD ternary complexes, metabolism, and pharmacokinetics.

4. The study investigated the complexation of quercetin (Que) and β-cyclodextrin (βCD) in alcoholic solutions using UV spectroscopy. Three different aqueous media were used to vary environmental conditions and interaction between host (βCD) and guest molecules (Que): pH 3, nondenaturing (pH 5.5), and pH 7. The equilibrium constants for the formation of the embedded βCD-Que complex were estimated from the different absorption bands, and the thermodynamics of the complexation were discussed.

5. The rapid detection and enrichment of polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) pose significant challenges in environmental science. This paper investigates the combination of 2,3,7,8-tetrachlorobenzo-di-dioxin (TCDD), a representative PCDD molecule, with -cyclodextrin (?-CD), a widely used compound in supramolecular chemistry, through quantum chemistry (QM) calculations and molecular dynamics (MD)

simulations. The results show that a stable inclusion complex can form in both gas and solvent phases, indicating that ?-CD could potentially serve as a layer for TCDD enrichment. The calculated vibration spectra suggest that infrared and Raman spectroscopy may be suitable for detecting TCDD-modified CDCD. The current theoretical findings may be informative to environmental scientists who are dedicated to developing effective methods for detecting and treating persistent organic pollutants.

3. Objectives:

1- Determine the best computational simulation between a natural coffee compound and a betacyclodextrin complex.
2- Determine the ratio of the natural coffee compound to the ratio of the betacyclodextrin complex.
3- Determine the best model between the natural coffee compound and the betacyclodextrin complex.
4- Calculating the best practical weight ratio between the two compounds to obtain a healthy product for consumption.

4. Applied methods and programs used:

Chemical computing:

Computer chemistry offers a wide range of possibilities, often involving multiple disciplines due to the significant advancements in computer and software capabilities. It also integrates with chemistry curricula [12]. Another application of computer chemistry is to gain a

comprehensive understanding of a problem. Experimental chemists frequently employ computer chemistry technology to enhance their understanding of the systems they study. [13]

Computational chemistry has various applications, including designing molecular systems before synthesising them in the laboratory. [14] Although computational models are not perfect, they can eliminate up to 90% of potential compounds as unsuitable for their intended use. This information is valuable as synthesising a single compound can take months of labour and raw materials, and produce toxic waste.[15]

4.1. Technical Details:

The calculations were performed on an Intel CORE i3 3.0 Hz workstation with dual OS and 64-bit Windows 7. Gaussian 03 [16] was used to implement the quantum mechanics of compilers in a vacuum, while the interface of complex complexes was implemented using Hyperchem Molecular Modeling software (version 8.0). Minimization was performed using the conjugate gradient algorithm with 1 cal/mol and reduced to 100 cal/mol.

4.2. Quantum Mechanics Calculation:

The structures of the complexes were initially generated from crystallographic parameters provided by Cambridge Structural and then optimized separately using the semiempirical method, PM3, with the Gaussian03 software package [16]. The combined complexes' starting geometries were constructed using HyperChem (version 8.0, Hypercube, Gainesville, FL, USA).

This study employed programs based on quantum mechanical equations and their approximations.

1. Hyper Chem Professional-08 :

Hypercube Inc. has developed a versatile molecular optimizer with a powerful computing package that provides numerous molecular models and quantum mechanical calculations.[17]

2. Gaussian-03:

A program for calculating energy was used to study molecular structures and the vibrational frequency of molecular systems, as well as stable and unstable interactions [18].

The programs were installed on a Lenovo laptop with a 32-bit Windows 7 Professional operating system, 2 GB of memory, and standard device speed. All calculations were performed on this device.

4.3. Method of work :

The initial step involves drawing the molecular structure of β-CD and Coffee.

The chemical formulas for these molecules were obtained from the Cambridge Structural Database (CSD) and were constructed and visualised using GaussView software. The structures were then optimised using the COMPUTE Geometry Optimization method in Hyper Chem Professional.

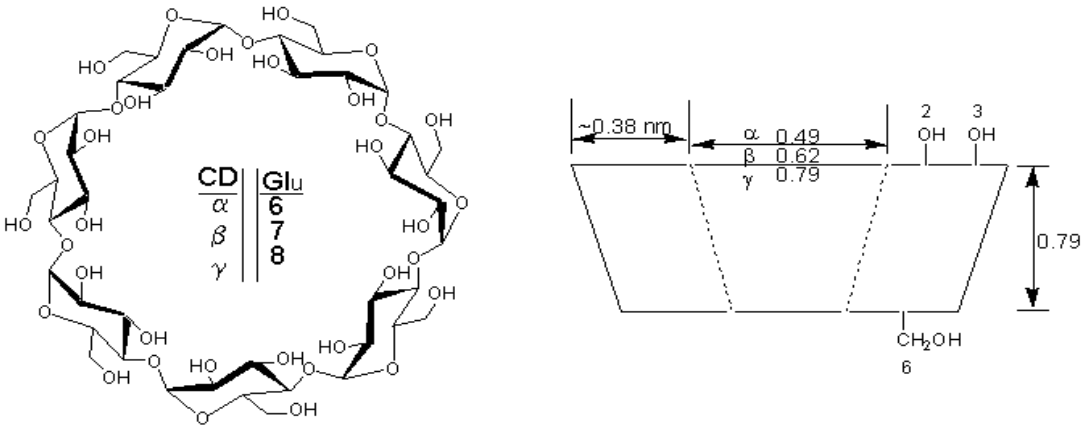


Figure 3. Structural formula of beta-cyclodextrin β _CD

Computational model of caffeine complex

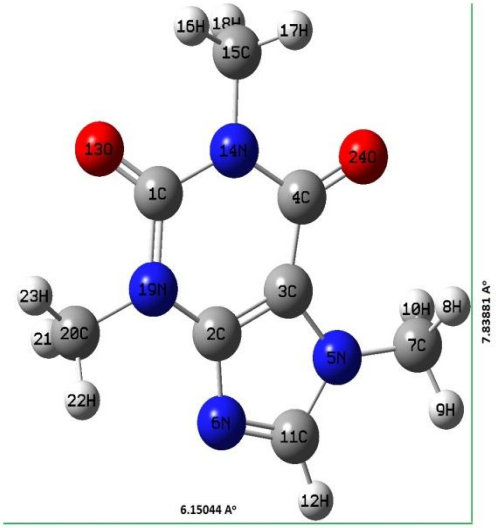
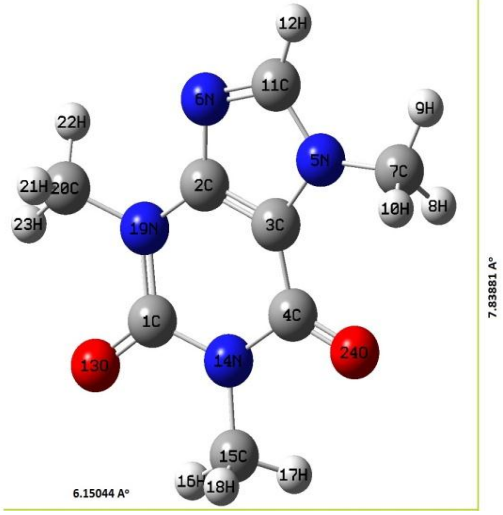
Model A	Model B
	

Figure 4. Structural formula of models A and B of the caffeine compound.

The combination resulted in two models: Model A, where the allene from the (CH3) group was inserted into the cavity of _CD β, and Model B, where the allene from the (CH) group was inserted into the cavity of _CD β. The

models were generated through random simulation using the G03 program to calculate the best possible model.

4.4. Calculation method :

The external power voltage calculation followed these steps using the Gaussian03 program.

Method-------Semi empirical-------PM3

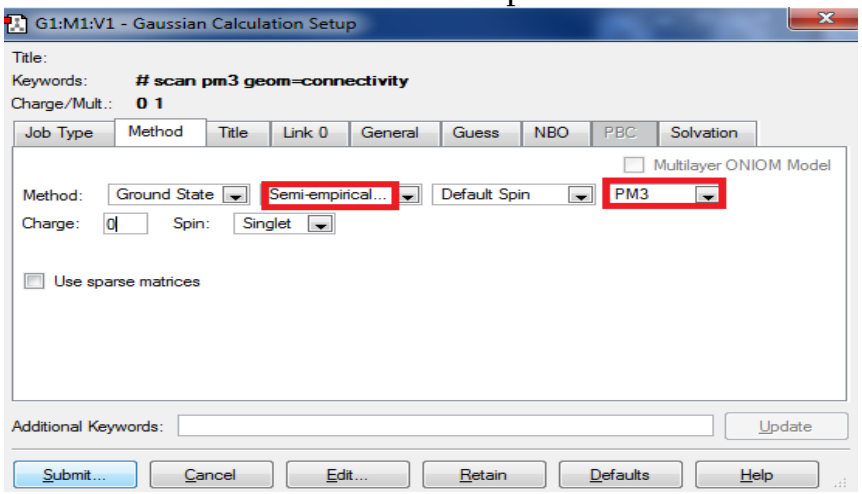


Figure 5. Calculation window for Gaussian software.

Semi empirical:

Semi-experimental methods combine quantum physics with experimental measurements. Several approximations were made to expedite calculations, making them faster than (ab initio) mathematical calculations. The most commonly used methods are PM3, NNDO, and AM1, which are used to study molecular and atomic energies and binary momentum. The electrode, electronic spectra, and other properties are suitable methods for studying medium-sized systems (hundreds of atoms) and systems that involve electronic transfer.

PM3:

Parameterization method 3 is a three-dimensional scale in space with the x, y, and z axes. It is one of the most commonly used semi-empirical methods for organic systems. This method is employed to calculate the enthalpy of formation, total energy, bond lengths, and hydrogen bond angles. Compared to other semi-empirical methods used for the same calculations, such as MP1 and MNDO, it is more accurate.

5. Results and discussion:

In Model A, Design-4, the study found that the betacyclodextrin compound can effectively contain two caffeine compounds in a stable and active state.

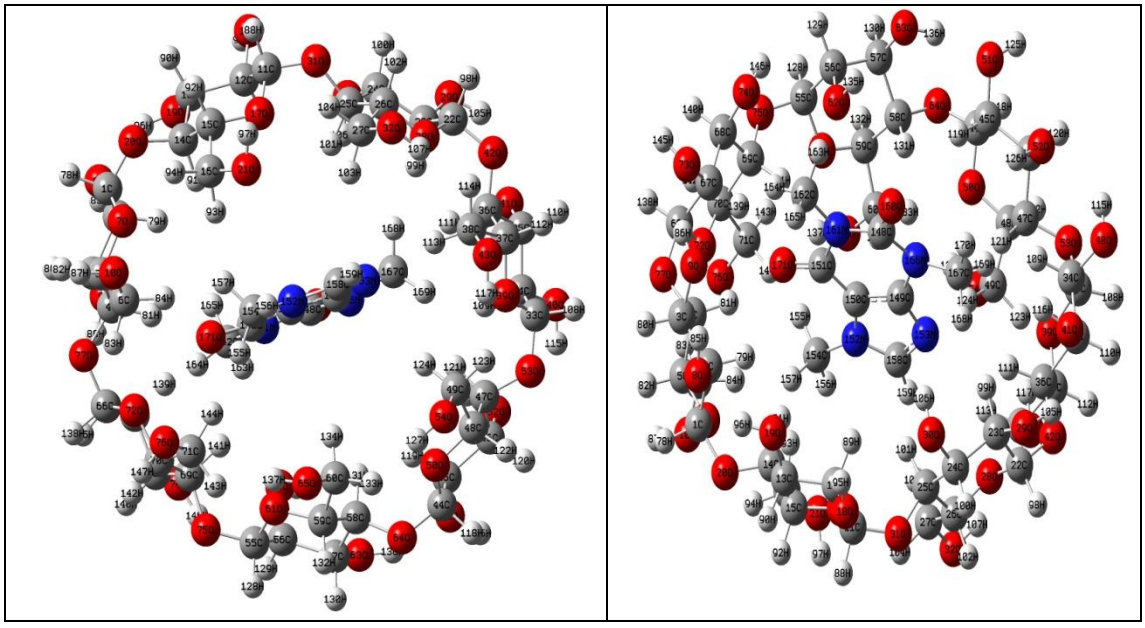


Figure 6: Molecular modeling of the caffeine compound intercalation of **Design 4** of Model **A** within a betacyclodextrin cavity.

Design 4 of Model A exhibited the best internal energy overlap and stability compared to the other designs listed in Table 1.

Table 1 shows the internal energy of the compound of betacyclodextrin and caffeine, as well as the combined models between caffeine as a guest compound and betacyclodextrin as a host compound.

Complex name	Scan energy/ kcal/mol	Optimization energy/ kcal/mol	Statues
B-CD	-1283.015933	-1439.585856	Highest
Coffee	- 49.1335630	-49.34810858	Highest
Design-1-	-1332.804491	-1498.194939	Highest
Design-2-	-1332.428550	-1496.972174	Highest
Design-3-	-1257.253652	-1500.299920	Highest
Design-4-	**-1278.916476**	**-1500.334998**	**Lowest**
Design-5-	-1331.459801	-1498.766475	Highest
Design-6-	-1331.813339	-1496.114619	Highest
Design-7-	-1033.142737	-1495.440423	Highest

The results show that the improvement energy for the compounds individually and together in the form of listed complexes is lower than the energy of the external scan. Therefore, in this study, we will rely on the improvement energies. The best improvement energy for the listed complexes was lower than that of the compounds alone, making them more stable among the models. The fourth form of the listed complex had the lowest bonding energy and was the most stable.

Multiple compounds will be added to coffee with beta-cyclodextrin as the primary host to determine if the bonding energy is improved and more stable or vice versa. The fourth complex listed will be used to determine the

optimal number of water molecules needed. The goal is to achieve the lowest and highest enhancement bond energy among all listed complexes.

The specific compound included in the fourth listed complex was betacyclo. This is shown in Table 2. Two coffee compounds were added to a compound or complex, resulting in a lower bonding energy and increased stability compared to the betacyclo complex alone. According to the industrial recipe, the best form of Betacyclo is in a 1:2 ratio with the natural coffee compound. This results in a product with a sweet taste that is ready for immediate consumption.

Table 2: shows a comparison of the internal energy of a compound of betacyclodextrin and caffeine in the case alone with caffeine and in the case of two caffeine compounds.

Complex name	1 Caffeine : 1 B_cyclodextrin	2 Caffeine : 1 B_cyclodextrin
Design-4-	-1500.334998	-1543.726347

Figures 7 and 8 demonstrate the stability of the fourth form of the betacyclodextrin complex with caffeine, which exhibits stable and consistent activity.

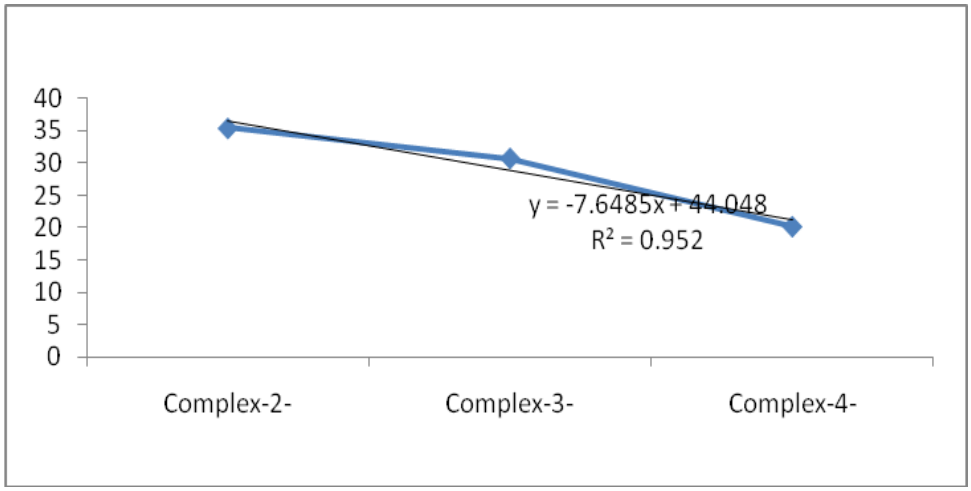


Figure 7: shows the activity curve between the complexes.

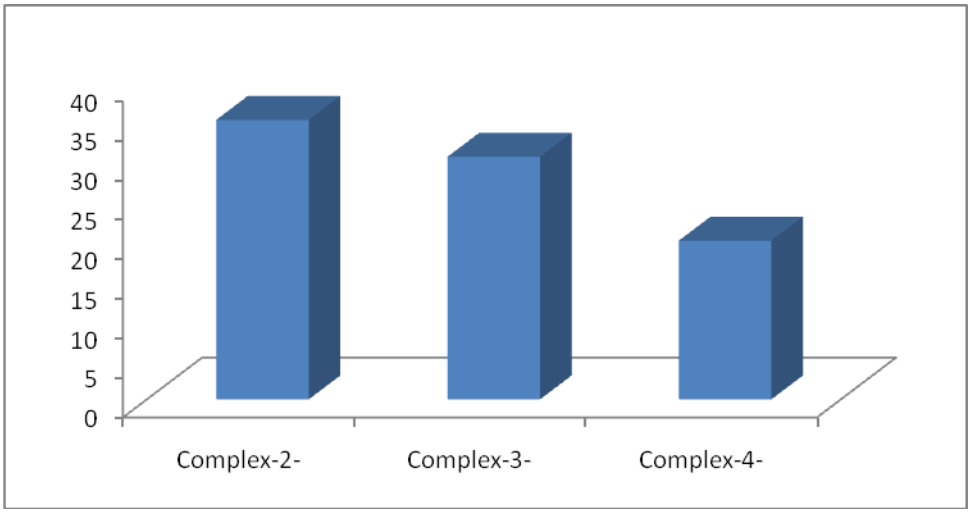


Figure 8: shows the percentage increase in activity between the complexes.

6. Conclusion :

It has been concluded that the betacyclodextrin complex can contain two caffeine compounds with stable energy and good activity. The highest level of interaction was observed at an internal energy of -1543.726347 Kilocalorie. The computational analysis suggests that the second complex is more active and vital in the outer environment

of microorganisms, while the other complexes vary in their connection energy and stability.

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